REMARKS

Claims 1, 11, and 12 have been amended to more clearly describe the compound of formula (I). Support for the amendments can be found, for example, at page 11, lines 17-20, and at page 16, lines 23-24 of the specification. Claim 9 has been cancelled. No new matter has been added. The Examiner has indicated the allowability of claims 1-7 and 10-11 over the prior art.

Election/Restriction

The Examiner has determined that there has been a constructive election of subject matter in which Y is -CO-, and that subject matter where Y is $-CH_2-$ or $-SO_2-$ is withdrawn. See page 2 of the Office Action. Claims 1, 11 and 12 have been amended accordingly. Claim 9 has been cancelled.

Rejections under 35 U.S.C. § 101 and 35 U.S.C. § 112, first paragraph

The Examiner has applied a new 35 U.S.C. § 112, first paragraph rejection in conjunction with a 35 U.S.C. § 101 rejection. See pages 3 and 7 of the Office Action. Briefly, the Examiner argues that claims 12-14 are not supported by a specific and substantial utility or a well established utility, and therefore one skilled in the art would not know how to use the invention. Applicants respectfully disagree. The methods of claim 12-14 are useful, and a person skilled in the art would know how to use the methods.

In rejecting claims 12-14 under 35 U.S.C. § 101, the Examiner argues that a method of "'preventing, inhibiting or suppressing cell adhesion' is not equivalent to a positive recitation of how to use the product for the treatment of a particular disease of real world relevance." See the Office Action at page 7. There is no requirement that a method claim act as "a positive recitation of how to use [a] product." Nor is there any requirement for Applicant to show that the compounds recited in claim 12 can be used in "treatment of a particular disease of real world relevance." To comply with 35 U.S.C. § 101, the methods of claims 12-14 need a specific and substantial asserted utility or a well established utility, and no more. See, for example, MPEP 2107 II(B)(1) (emphasis added):

> If the applicant has asserted that the claimed invention is useful for any particular practical purpose... and the assertion would be considered

> credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility.

A specific and substantial utility for the methods of claims 12-14 is asserted in the specification. See, for example, page 4, lines 11-24 ("These compounds are useful for inhibition, prevention, and suppression of VLA-4-mediated cell adhesion and pathologies associated with that adhesion.... This invention also provides... methods of using the compounds.") In addition, the specification provides additional support for the credibility of this assertion. See, for example, page 2, lines 25-31:

> Results of in vivo experiments suggest that this inhibition of VLA-4-dependent cell adhesion may prevent or inhibit several inflammatory and autoimmune pathologies (R.L. Lobb et al., 'The Pathophysiologic Role of α4 Integrins In Vivo', J. Clin. Invest., 94, pp. 1722-28 (1994)).

A copy of the Lobb reference cited above is enclosed with this reply (attached at Tab 1). A person of ordinary skill in the art would understand from the Lobb reference, and other references cited in the specification, that the asserted utility was a well-established utility at the time the application was filed.

The Examiner has stated that "unless the pathway at issue is critical to treating some condition, and the pathway modification and disease treatment are inexorably linked, such pathway modification is devoid of utility" (Office Action at pages 7-8). Applicants respectfully disagree. Applicants have asserted a specific, substantial, and well-established utility. Thus, claims 12-14 meet the requirements of 35 U.S.C. § 101.

In conjunction with the rejection under 35 U.S.C. § 101, the Examiner has also rejected claims 12-14 under 35 U.S.C. § 112, first paragraph, as being "reach-through claims. The claims are directed to a method of preventing, inhibiting, or suppressing cell adhesion in a mammal, yet these claims does [sic] not meet the requirements for 'how to use' under 35 U.S.C. § 112, first paragraph." See page 3 of the Office Action. A person of skill in the art reading the specification would clearly understand how to prevent, inhibit or suppress cell adhesion in a mammal by administering to the mammal a pharmaceutical composition comprising an effective amount of a cell adhesion inhibitory compound of formula (I). See pages 28-32 of the

specification. The claimed method is adequately enabled by the specification; the Examiner has not provided a *prima facie* case that it is not.

Applicants respectfully request that the rejections of claims 12-14 under 35 U.S.C. § 101 and 35 U.S.C. § 112, first paragraph, be reconsidered and withdrawn.

Rejection under 35 U.S.C. § 112, first paragraph

Claims 12-15 have been rejected by the Examiner under 35 U.S.C. § 112, first paragraph, as not being enabled. Claim 12 is independent, and claims 13-15 depend from it.

In the Office Action mailed February 12, 2004, the Examiner applied a rejection under 35 U.S.C. § 112, first paragraph, and specifically stated: "Applicants can overcome this rejection by including the phrase 'in need thereof' after 'in a mammal' in line 2 of claim 12." See page 3 of the Office Action mailed February 12, 2004. In responding to that Office Action, Applicants amended claim 12 accordingly, with the understanding from the Examiner's remarks that the amendment would put claim 12 (and the claims depending from it) in condition for allowance. The Examiner has instead maintained the 35 U.S.C. § 112, first paragraph rejection, alleging that "the 'laundry list' of diseases and conditions encompassed by claims 12-15 is not enabled." See the Office Action at page 3. Applicants respectfully disagree.

Applicants have discovered a method of preventing, inhibiting or suppressing cell adhesion in a mammal in need thereof. The method includes administering to the mammal a pharmaceutical composition including an effective amount of a cell adhesion inhibitory compound. See claim 12, which recites in part:

> A method of preventing, inhibiting or suppressing cell adhesion in a mammal in need thereof comprising the step of administering to said mammal a pharmaceutical composition comprising an effective amount of a cell adhesion inhibitory compound of formula (I)....

The Examiner appears to be under the impression that claim 12 is directed to a method of treating a disease. See page 4 of the Office Action, where the Examiner states: "The nature of this invention is of methods of treating many different unrelated diseases or conditions." The

Examiner also referred to "any and all cell-adhesion associated diseases encompassed by the claims" and "said diseases may be listed on pages 37-38 of the specification." See page 3 of the Office Action. Furthermore, in the Office Action, the Examiner refers repeatedly to diseases that are within the scope of claims: "all the diseases claimed," (page 5); "treatment of the claimed distinct diseases," (page 5); "method of treating all claimed diseases," (page 5); and "treating all of the claimed diseases," (page 6). Finally, in concluding the rejection under 35 U.S.C. § 112, first paragraph, the Examiner states: "the specification fails to provide sufficient support of the broad use of the compound of the claim 1 for the treatment of all claimed diseases." See the Office Action at page 7. Although the Examiner refers to the compound of claim 1, Applicants address the rejection of claim 12.

The method of claim 12 is **not** directed to a method of treating a disease. It is directed to a method of preventing, inhibiting, or suppressing cell adhesion in a mammal. As such, the question of whether claim 12 is enabled centers on whether the specification provides an enabling disclosure of the subject matter **encompassed by claim 12**. Specifically, claim 12 is directed to a method of **preventing, inhibiting or suppressing cell adhesion** in a mammal in need thereof including the step of administering to said mammal a pharmaceutical composition comprising an effective amount of a cell adhesion inhibitory compound of formula (I). See claim 12. The question of whether or not a person practicing the methods of claim 12 would be able to treat a disease is irrelevant.

The specification describes how the compounds may be used to prevent, inhibit, or suppress cell adhesion, for example, at pages 28-32. In particular, prevention, inhibition, or suppression of cell adhesion in a mammal is discussed at page 31, line 4 - page 32, line 8. The specification also provides working examples of such prevention, inhibition, or suppression of cell adhesion in a mammal, for example at page 123, line 20 to page 125, line 31. Based on the teachings of the specification, a person of ordinary skill in the art would be able to use the methods of claims 12-15. No undue experimentation is required. Therefore, claim 12 is enabled.

The Examiner considered the *Wands* factors (*In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404) in determining whether experimentation required to practice an invention is undue. We address the Examiner's comments regarding the *Wands* factors below.

The nature of the invention

As discussed above, the nature of the invention is a that of a method of preventing, inhibiting, or suppressing cell adhesion in a mammal, and is not, as the Examiner suggested, "treating many different unrelated diseases or conditions."

The state of the prior art

The Examiner notes that "treatment of disease or symptoms are not analogous terms." See page 4 of the Office Action. Applicants note again that claim 12 is not directed to treatment of disease, nor to treatment of symptoms, but is directed to a method of preventing, inhibiting, or suppressing cell adhesion.

The Examiner has also indicated that "the diseases recited within claims 14 and 15 are not the same but different diseases," specifically arguing that psoriasis, diabetes, inflammatory bowel disease, and asthma are not autoimmune diseases. Claims 14 and 15 each depend from claim 12. It is therefore irrelevant whether elements recited in these two claims are the same or different, as long as the elements fall within the scope of independent claim 12. In addition, Applicants point out that claim 14 refers to a **cell adhesion-associated immune or autoimmune** response. Furthermore, psoriasis, diabetes, inflammatory bowel disease, and asthma are immune or autoimmune diseases. Applicants have enclosed with this reply copies of publications by the National Institute of Allergy and Infections Diseases. One, entitled "Asthma Basics" (http:// www2.niaid.nih.gov/ Newsroom/FocusOn/Asthma01/basics.htm#what, accessed August 24, 2004, attached at Tab 2) describes asthma as "an allergic reaction" in which "the immune system goes into high gear." The second, titled "What Are Some Examples of Autoimmune Diseases?" (http://www.niaid.nih.gov/publications/ autoimmune/examples.htm, accessed August 24, 2004, attached at Tab 3) lists psoriasis, diabetes, and inflammatory bowel disease as examples of autoimmune diseases.

The predictability or lack thereof in the art

In discussing predictability in the art, the Examiner remarks on the complexity of the immune response and the lack of absolute predictability in the pharmaceutical arts. The Examiner concludes that "in the absence of a showing of correlation between all the diseases claimed as capable of being treated by the compound of claim 1 and the inhibition of VLA4-mediated cell adhesion, one of skill in the art is unable to fully predict possible results from the administration of the compound of claim 1." See the Office Action at page 5. Applicants stress that compounds of claim 1 are not at issue. The methods of claims 12-15 are subject to the 35 U.S.C. § 112, first paragraph rejection. Applicant's remarks therefore concern claims 12-15.

There is no need for a showing of correlation between diseases and inhibition of VLA-4 mediated cell adhesion, because claim 12 is directed to a method of preventing, inhibiting or suppressing cell adhesion in a mammal in need thereof, not to a method of treating a disease. Compounds of claim 12 are cell adhesion inhibitors, as supported by experimental results provided in the specification (see, for example, the examples at pages 116-125). Moreover, "VLA4-associated cell adhesion plays a central role in a variety of inflammation, immune and autoimmune diseases," according to the specification (see page 38, lines 1-2). The level of predictability in the art is such that a person of ordinary skill can predict that administering a pharmaceutical composition comprising an effective amount of a cell adhesion inhibitory compound of formula (I) to a mammal will result in prevention, inhibition or suppression of cell adhesion in the mammal.

The amount of direction or guidance present

The Examiner argues that the "efficacy of an individual compound against a specific disease or symptom needs to be specifically and individually supported by factual evidence." This argument does not address the question of enablement of claim 12, because claim 12 is directed to a method of preventing, inhibiting or suppressing cell adhesion, not to a method of treating a disease. There is extensive experimental evidence showing that individual compounds (that are within the scope of formula (I) as defined in claim 12) can prevent, inhibit or suppress cell adhesion. See, for example, the table at pages 118-120, listing IC_{50} results for more than 150 individual compounds.

The presence or absence of working examples

The Examiner has noted that the specification discloses *in vitro* and *in vivo* working examples, for example at pages 116-126. However, the Examiner regards these examples as "insufficient evidence for methods of treating all claimed diseases." Applicants again ask that claim 12 be examined with respect to its proper scope, defined by the claim itself: a method of preventing, inhibiting or suppressing cell adhesion in a mammal in need thereof. The working examples are evidence that claim 12, and the claims depending from it, are enabled.

The breadth of the claims

Applicants rebut the Examiner's notion that "Applicants are claiming methods of treating a broad number of diseases that are unrelated" (Office Action at page 6). As discussed above, claim 12 is directed to a method of preventing, inhibiting or suppressing cell adhesion.

The quantity of experimentation needed

The Examiner contends that "[o]ne of skill in the art would need to determine what listed diseases would be benefited by the stimulation of cannabinoid receptors." See the Office Action at page 6. Nothing in the specification or claims has any relationship to the stimulation of cannabinoid receptors. Nevertheless, Applicants contend that the specification provides enabling disclosure of the method of preventing, inhibiting or suppressing cell adhesion as recited in claim 12, and that any experimentation required to practice the methods of claims 12-15 is not undue.

The level of skill in the art

According to the Examiner, even though skill in the art is high, "each embodiment... is required to be assessed for physiological activity... to determine which compounds exhibit the desired pharmacological activity and which diseases would benefit from this activity." See the Office Action at pages 6-7. The specification provides experimental evidence of which compounds can inhibit cell adhesion (e.g, the table at pages 118-120). This information and the general disclosure of the specification is sufficient to provide enablement of claim 12. Any discussion of what diseases can benefit from the inhibition of cell adhesion is not pertinent to enablement of claim 12.

Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. § 112, first paragraph.

CONCLUSION

Applicants ask that all claims be allowed. Please apply any deposits or credits to Deposit Account No. 19-4293.

Respectfully submitted,

Date: 9-28-04

Harold H. Fox
Reg. No. 41,498

Steptoe & Johnson LLP
1330 Connecticut Avenue, NW
Washington, DC 20036-1795
Phone: 202-429-3000
Fax: 202-429-3902

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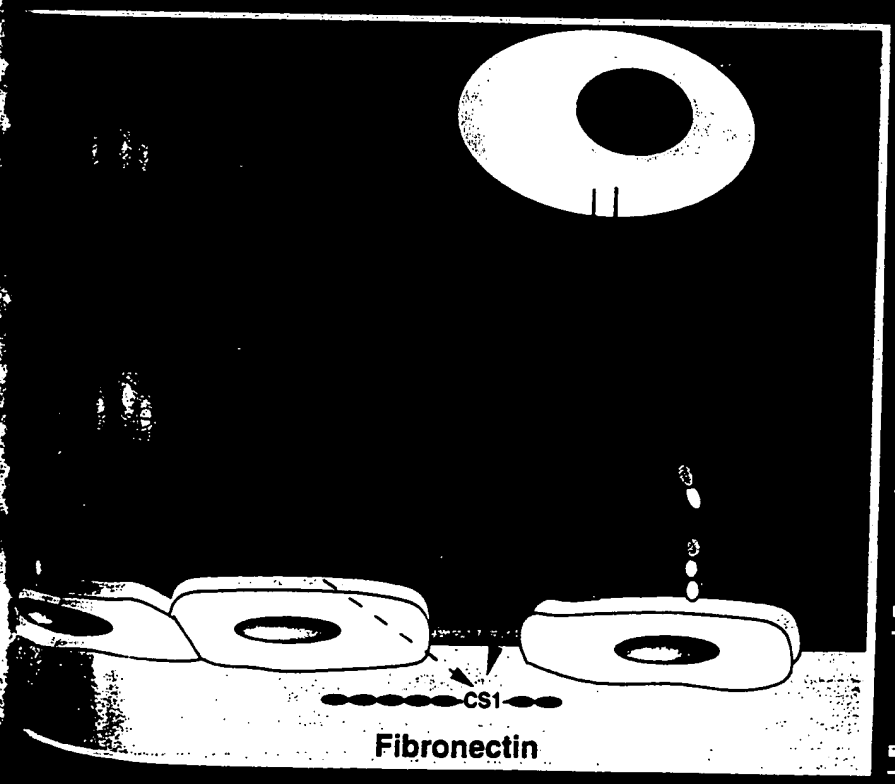

- molecular medicine / genetic disorders
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- hormones / cytokines / signaling
- cell growth & differentiation
- cellular, transport & organ physiology
- atherosclerosis / thrombosis / metabolism

The Pathophysiologic Role of $\alpha 4$ Integrins In Vivo

Roy R. Lobb* and Martin E. Hemler‡
* *Biogen, Inc., Cambridge, Massachusetts 02142; and* ‡ *Dana Farber Cancer Institute, Boston, Massachusetts 02115*

Introduction

The integrins $\alpha 4\beta 1$ (very late antigen-4; VLA4; CD49d/CD29)[1] and $\alpha 4\beta 7$ are cell surface heterodimers expressed mostly on leukocytes. The VLA4 molecule, initially characterized on lymphoid cells, was subsequently shown to mediate cell adhesion to vascular cell adhesion molecule-1 (VCAM1) (CD106), as well as to an alternately spliced form of the extracellular matrix protein fibronectin (Fn) (for review see references 1–4). VCAM1 was originally described as an inducible endothelial cell adhesion molecule, but has subsequently been found to be constitutively or inducibly expressed on many other cell types (2, 3). The integrin $\alpha 4$ can associate with another β subunit, first called βP in the mouse (5) and now designated $\beta 7$. Integrin $\alpha 4\beta 7$ appears central to lymphocyte homing to intestinal tissue via adherence to the gut homing receptor mucosa addressin cell adhesion molecule (MadCAM) (6) and binds also to VCAM1 and Fn (7, 8). These functional activities defined in vitro suggested that $\alpha 4$ integrins might play critical roles in migration of leukocytes into tissues at sites of inflammation.

In the past few years specific monoclonal antibodies which block $\alpha 4$-dependent adhesive function in vitro have been tested in vivo. In 1991 and 1992, only a few papers were published using such mAbs, but in 1993 there were 15, with many more either published or in press so far this year (Table I). Here we review these rapidly accumulating in vivo data which suggest that $\alpha 4$ integrin–dependent adhesion pathways are critical intervention points in several inflammatory and autoimmune pathologies. To save space we have been unable to cite all original references, but these can be found within either recent reviews (2–4) or the more recent references given.

Overview of $\alpha 4$ integrin distribution and in vitro functions

The VLA4 integrin is expressed at substantial levels on most mononuclear leukocytes, whether in circulation, within lymphoid organs, or resident in other tissues (1). Also it is found on eosinophils, basophils (9), and various nonhematopoietic tumor cells (e.g., rhabdomyosarcoma, melanoma). The $\alpha 4\beta 7$ integrin is expressed on most lymph node T and B cells (10), on the gut homing subset of $CD4^+$ memory T cells (11), and on lymphocytes resident in rheumatoid synovium (12). Recent studies show that natural killer cells, eosinophils, and newborn blood B and T cells show relatively homogeneous expression of $\alpha 4\beta 7$, while adult blood B cells and $CD8^+$ T cells, like $CD4^+$ T cells, show more heterogeneous expression (13). Finally, the $\alpha 4$ subunit (with unspecified β) is found in several nonlymphoid tissues in the developing embryo, including vascular smooth muscle and skeletal muscle (14, 15).

VLA4 recognizes a motif containing the sequence EILDVPST within the alternately spliced connecting segment 1 (CS1) region of Fn (3), with the LDV sequence being the most critical (16). VLA4 binds to sites within the first and fourth immunoglobulin-like domains of the full-length seven-domain form of VCAM1 (17, 18). Within domain one, a QIDSPL motif appears to be critical to integrin recognition (19, 20). Within the VLA4 molecule, binding sites for the CS1 region of Fn and for VCAM1 are overlapping, as evidenced by antibody cross-blocking (21) and competitive binding studies (22). However, these binding sites have distinct features, since the VLA4 interaction with VCAM1 but not Fn is supported by calcium ions (23) and some antibodies selectively inhibit only the latter adhesive interaction (24).

A number of weaker VLA4 interactions have been reported, for example with the Fn HepII (25), CS5 (26), and RGD (27) sequences, as well as with thrombospondin (28), but these interactions generally require VLA4 to be highly activated and their in vivo relevance remains to be determined. VLA4 (among other integrins) also interacts with the bacterial coat protein invasin (23, 29).

The $\alpha 4\beta 7$ ligands Fn, VCAM1, and MadCAM apparently bind to overlapping sites within the $\alpha 4\beta 7$ molecule, but these three interactions respond quite distinctly to regulatory antibodies and divalent cations (6, 11). The complete absence of any VLA4 reactivity with MadCAM (6) implies a distinct role for the $\beta 7$ chain not shared by the $\beta 1$ chain.

Like other integrins, both VLA4 and $\alpha 4\beta 7$ can exist in a range of activation states, depending both on cell type and on the extent of triggering by various cellular agonists such as phorbol esters, anti-CD3 antibodies, chemokines, and chemotaxis factors (6, 23, 30–32). Whereas VCAM1 has a low threshold of activation (23) and can support constitutive adhesion by PBLs (33), adhesion to Fn requires a higher level of activation (23, 34), thus reducing constitutive interaction between blood cells and soluble Fn in plasma. Cells bearing $\alpha 4\beta 7$ adhere avidly to MadCAM (6).

The cytoplasmic domain of $\alpha 4$ plays a key role in regulating cell adhesion (35), with the five to six residues just after the

Biogen, Inc. has a commercial interest in the development of VLA4-based therapeutic.

Address correspondence to Dr. Roy Lobb, Biogen, Inc., 14 Cambridge Center, Cambridge, MA 02142.

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1. *Abbreviations used in this paper:* AHR, airways hyperresponsiveness; BAL, bronchoalveolar lavage; CS, connecting segment; DTH, delayed-type hypersensitivity; EAE, experimental allergic encephalomyelitis; Fn, fibronectin; MadCAM, mucosal addressin cell adhesion molecule; NOD, nonobese diabetic; VCAM1, vascular cell adhesion molecule-1; VLA, very late antigen.

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Table I. In Vivo Studies with mAbs to α4 Integrins

Type of study	Species	mAb	Reference
Cell recruitment			
Lymphocyte	Mouse, rat	R1-2, PS/2, TA-2, HP2/1	58, 59, 66–68, 71, 74–77
Eosinophil	Guinea pig	HP1/2	60, 71, 82, 83
Monocyte	Rabbit	HP1/2	61, 95
PMN	Rat, rabbit	TA-2, HP1/2	61, 69
Disease model			
Lung antigen challenge	Mouse, rat, guinea pig, sheep	PS/2, TA-2, HP1/2	62, 71, 81–83
Ulcerative colitis	Primate	HP1/2	63
EAE	Mouse, rat	R1-2, HP2/1	59, 67
Contact hypersensitivity	Mouse	R1-2, PS/2	72, 73
Diabetes	Mouse	R1-2, PS/2	74–76
Nephritis	Rat	HP2/1, TA-2	79, 80
Allograft rejection	Rat, rabbit	TA-2, HP1/2	70, 95
Other studies			
Progenitor mobilization	Primate	HP1/2	64
Intestinal infection	Rat	TA-2	91
Gut homing	Mouse, rat	R1-2, PS/2, DAK32, TA-2	58, 77

transmembrane region being most critical (36). Compared with VLA4, the $\alpha4\beta7$ integrin may have specialized regulatory features, including a greater requirement for phorbol ester stimulation (7, 8), and distinctive regulation through the $\beta7$ cytoplasmic domain (37).

Adhesion through VLA4 can lead to a wide spectrum of subsequent events. Both Fn and VCAM1 can act through VLA4 to deliver costimulatory signals (together with anti-CD3/T cell receptor) leading to T cell proliferation and cytokine production (38, 39). Likewise, adhesion through VLA4 may promote (40) or inhibit (41) cell death, depending on the lymphoid cell type and other conditions; triggering through VLA4 can regulate expression of genes for T cell 72-kD gelatinase (42), and monocyte inflammatory mediators (43), and may trigger tyrosine phosphorylation of a 105-kD protein in lymphocytes (44, 45). A further consequence of VLA4/ligand interaction is the transendothelial migration of monocytes (46, 47), the random migration of lymphocytes through filters coated with VCAM1 or Fn (48), and the migration of lymphoma cells beneath stromal cells (49). Consistent with these results, the α4 cytoplasmic domain may be particularly well suited to support cell migration (50).

α4 integrin structure and mAb epitopes

The α4 gene encodes a 150-kD protein and has been cloned from both murine and human sources (51, 52). Its primary sequence shows most similarity (39%) to the integrin α9 subunit (53). The mature 150-kD α4 protein can be variably cleaved into 80- and 70-kD fragments, but this cleavage does not alter adhesive functions (54). Another unusual feature of α4 is a conformational rearrangement, dependent on divalent cations and certain critical cysteines, that causes it to migrate at 180 kD instead of 150 kD in SDS gels (reference 55 and Pujades, C., and M. E. Hemler, manuscript in preparation).

The majority of monoclonal antibodies recognizing the human α4 subunit define three nonoverlapping epitopes (21). mAbs to epitope A partially block VLA4 adhesion to Fn but do not inhibit VCAM1 adhesion, whereas mAbs to epitope B effectively block adhesion to both ligands (as well as to invasin). Also, mAbs to epitope A and a subset of those to epitope B trigger homotypic aggregation (21). Epitope C mAbs have no effect on either adhesion or aggregation. Antibodies that recognize the human VLA4 (56) and $\alpha4\beta7$ (11) complexes have also been described and should prove useful in distinguishing the two heterodimeric forms. Both function-blocking and nonblocking anti-mouse α4 antibodies have also been defined, as well as an antibody, DAK32, that specifically recognizes the murine $\alpha4\beta7$ complex (6).

Importantly, mAbs that block adhesive function in vitro have now been characterized which work in all species, allowing in vivo studies to be performed in a variety of animal models (Table I). These include rat anti-murine α4 mAbs R1-2 and PS/2 (5, 57), both of which can induce homotypic aggregation (Holzmann, B., personal communication), murine anti-rat α4 mAb TA-2 (58), murine anti-human mAb HP2/1 (21), which binds and blocks rat α4 (59), and murine anti-human mAb HP1/2 (21), which binds and blocks guinea pig, rabbit, sheep, and primate α4 (60–64).

In vivo studies with mAbs to α4

mAbs to α4 block leukocyte recruitment. The identification of VLA4 as a counterreceptor for VCAM1 (65) suggested that this adhesion pathway might play a role in migration of VLA4-expressing cells from blood to tissues at sites of inflammation, and several studies have confirmed that this is indeed the case (58–61, 66–68). The earliest studies were those of Issekutz and co-workers (58, 66), who showed that the migration of ^{111}Indium-labeled rat lymphocyte subpopulations into inflammatory sites in the skin, both in response to cytokines and to a classic delayed-type hypersensitivity (DTH) reaction, and in the joints was α4 integrin dependent. In another study, eosinophil recruitment was evaluated (60) and mAb HP1/2 was found to block 50–80% of cellular recruitment into guinea pig skin in response to a variety of mediators and to a passive cutaneous anaphylaxis reaction.

The lack of expression of VLA4 on PMN suggests that

blockade of this integrin should not block acute PMN emigration and this is the case in several in vivo systems. For example, mAb HP1/2 does not block PMN recruitment at 4 h into rabbit peritoneum in response to protease peptone (61) and mAb TA-2 does not affect acute PMN-dependent complement-mediated lung injury in the rat (69). However, mAbs to $\alpha 4$ can affect PMN recruitment indirectly. For example, PMN-dependent edema is reduced in the mouse ear in T cell–dependent contact hypersensitivity (see below), and mononuclear leukocyte–dependent PMN recruitment into rabbit peritoneum is inhibited at 24 h after protease peptone administration (61).

Several studies have looked at the combination of $\alpha 4$ mAbs with either CD18-directed or lymphocyte function-associated antigen-1–directed mAbs (61, 68, 70, 71). Importantly, mononuclear leukocyte recruitment is almost completely abolished in the majority of models examined, independent of species, mAb used, or organ examined.

The data in many of these studies were interpreted to mean that VLA4 plays a critical role in leukocyte recruitment in vivo. However, with the increasing recognition that many leukocytes also express integrin $\alpha 4\beta 7$ (13), the relative role of each $\alpha 4$ integrin (as well as the nature of the counterligands involved) remains undefined in many systems and must be assessed in further studies (see following section). Nevertheless, the data argue that $\alpha 4$ integrins play a central role in leukocyte emigration from peripheral blood into inflammatory sites and that $\alpha 4$ and $\beta 2$ (CD18) integrins combine to coordinate leukocyte emigration into most tissues and organs in the body.

mAbs to $\alpha 4$ in rodent models of disease. mAbs to $\alpha 4$ have shown therapeutic effects in numerous rodent models of disease, including three classic models of T cell–dependent autoimmune disease. The first reports used rat and mouse models of experimental allergic encephalomyelitis (EAE) (59, 67), induced by passive transfer of $CD4^+$ myelin basic protein–specific T cell clones. After migration of these cells within 4–12 h into neural tissue and generation of an inflammatory response, hind limb and tail paralysis occurs at 4–5 d after injection. Yednock et al. (59) first showed that a single intraperitoneal injection of mAb HP2/1 on day 2 after passive transfer significantly delayed onset of paralysis in rats. The mAb had no effect on blood cell counts, and brainstems from control animals revealed extensive leukocyte infiltration, while such infiltration was absent from treated animals. Because the mAb was administered at day 2, i.e., after the entry of the T cell clones into neural tissue, it was proposed that mAb treatment blocked entry of host mononuclear leukocytes recruited nonspecifically to the site of inflammation. A second study in a mouse EAE model (67) confirmed and extended these results. These authors showed that the $CD4^+$ T cell clone could be further subdivided by phenotype. First, TH1 but not TH2 clones could induce disease. Second, induction of disease correlated with surface expression of $\alpha 4$ integrin. They found that coinjection of cells with either mAb R1-2 to $\alpha 4$ or mAb MK/1 to murine VCAM1 significantly delayed onset of paralysis. The data from both studies are consistent with VCAM1 on inflamed brain endothelium recruiting both antigen-specific T cells and nonspecific leukocytes into neural tissue via VLA4 (see below).

T cell–dependent murine contact hypersensitivity models (72, 73) also demonstrate a role for $\alpha 4$ integrins. Intravenous administration of either mAb R1-2 or PS/2 4–6 h before challenge inhibited 50–60% the ear swelling response of mice sensitized with either dinitrofluorobenzene or oxazalone (73). In a second study, mAb R1-2 blocked by ~ 80% the ear swelling induced by the adoptive transfer of trichloronitrobenzene-sensitized spleen cells (72). Interestingly, mAb R1-2 did not inhibit the overall emigration of either nonimmune or immune T cells (72), suggesting that in this model the mAbs do not function by inhibiting recruitment.

A third model of T cell–dependent autoimmune disease in which $\alpha 4$ mAbs have been evaluated is the nonobese diabetic or NOD mouse, which spontaneously develops type I diabetes, characterized by infiltration of pancreatic islets (insulitis) and destruction of insulin-producing islet cells. Three independent studies have shown that mAbs R1-2 (74–76) or PS/2 (75) both inhibit insulitis and delay significantly the onset of diabetes. mAbs MK/1 and MK/2 identify VCAM1 on inflamed but not normal islet vessels and also block onset of disease when used in vivo (75, 76).

A role for $\alpha 4\beta 7$ cannot formally be ruled out in these three models. However, recent studies show that, while mAb PS/2 blocks $\alpha 4\beta 7$-dependent lymphocyte adhesion in vitro and blocks lymphocyte homing to the gut, mAb R1-2 does neither (6, 77). In contrast, mAb R1-2 does block VLA4-dependent adhesion in vitro (8, 77). The efficacy of R1-2 in all three models, combined with the pan-lymphocyte distribution of VLA4 and the more restricted distribution of lymphocyte $\alpha 4\beta 7$, strongly argues that R1-2 is in fact a VLA4-specific mAb in vivo and that VLA4 is indeed the leukocyte receptor. The ability of mAbs to VCAM1 to block in the models in which they were tested (67, 75, 76) also points to VCAM1 as the VLA4 counterreceptor, at least on brain and islet endothelium.

In addition to these murine studies, mAb TA-2 has also been used in several rat models and has implicated $\alpha 4$ integrins in vascularized cardiac allograft rejection (70), immune complex–mediated lung injury (78), acute nephrotoxic nephritis (79), and in skin induration and fibrin deposition in DTH reactions (68). In addition, mAb HP2/1 significantly inhibits mercuric chloride–induced nephritis in Brown Norway rats (80).

mAbs to $\alpha 4$ in allergic lung inflammation. Several in vivo studies have now been performed in different species examining the role of $\alpha 4$ integrins in allergic airways (62, 71, 81–83). In a sheep model of allergic asthma (62), animals challenged with the parasite *Ascaris suum* undergo acute bronchoconstriction. Importantly, many animals then show a late phase response (LPR) 6–8 h after challenge, which correlates with eosinophil-rich leukocyte infiltration into the lung. mAb HP1/2 was highly effective at blocking the LPR, as well as the associated airways hyperresponsiveness (AHR) to carbachol (62). Nevertheless, inhibition of cellular recruitment could not fully explain the data, because bronchoalveolar lavage (BAL) leukocyte levels were affected to only a small degree by mAb treatment. Interestingly, aerosolized mAb HP1/2 was as effective as intravenous HP1/2 in blocking both the LPR and AHR, suggesting that the therapeutic effects in this model are due to mechanisms operative within the lung itself.

Consistent with the sheep data, treatment of ovalbumin-sensitized Brown Norway rats with mAb TA-2 just before challenge significantly blocked the LPR without significant changes in BAL leukocyte composition (81). In contrast, blockade of $\alpha 4$ integrin with mAb PS/2, or VCAM1 with mAb MK/1, significantly inhibited both eosinophil and T cell recruitment into the tracheas of ovalbumin-sensitized and challenged mice (71), which strongly express VCAM1 as assessed by immunohistology.

In ovalbumin-sensitized guinea pigs, Pretolani et al. (82) have shown that mAb HP1/2 effectively blocks AHR in response to carbachol after challenge. In this study, reduced eosinophil numbers are seen in BAL fluid. Immunohistologic studies of lung tissue show significantly reduced levels both of eosinophils and of both $CD4^+$ and $CD8^+$ T cells in the epithelial submucosa and adventitia (82). However, another study (83) found that, despite reduced eosinophil numbers and eosinophil basic peroxidase levels in the BAL of HP1/2-treated animals, the mAb had no effect on AHR to acetylcholine. The reasons for this discrepancy are unclear at present.

Taken jointly, the data argue that $\alpha 4$ integrins likely play multiple complex roles in lung pathobiology, including both recruitment and adhesion-dependent priming or activation of leukocytes and that $\alpha 4$ integrin-dependent adhesion pathways may prove to be suitable intervention points for allergic asthma.

mAbs to $\alpha 4$ in inflammatory bowel disease. The cotton-top tamarin is a New World primate that experiences a spontaneous chronic colitis marked by periodic flares of acute inflammation that closely mimics human ulcerative colitis, one of the two major forms of inflammatory bowel disease (63). Animals were treated during acute flares with mAbs to either E-selectin or $\alpha 4$ integrins. While no significant reduction in colitis activity was seen with two mAbs to E-selectin, the animals treated with mAb HP1/2 showed a highly significant attenuation of their colitis, as assessed histologically, and a statistically significant increase in weight.

mAbs to $\alpha 4$ peripheralize progenitor cells. Cellular interactions between hematopoietic cells and their stromal microenvironment in bone marrow are known to be central to their programmed maturation. Interactions between $\beta 1$ and $\beta 2$ integrins and their known ligands expressed on the earliest stem and progenitor cells have been implicated on the basis of in vitro studies (for review see reference 64). Recently, treatment of primates with blocking mAbs to CD18 or $\alpha 4$ have provided insight into the functional role of these adhesion pathways in vivo (64). Anti-$\alpha 4$ treatment, but not anti-CD18 treatment, resulted in a 100-fold selective mobilization of progenitors into the bloodstream. Peripheralization involved erythroid, myeloid, and mixed progenitors, was detectable 24 h after injection, and lasted beyond the final injection. In contrast, anti-$\beta 2$ treatment had no effect on the numbers of peripheral progenitors, despite increasing PMN counts significantly, demonstrating efficacy of the mAb. Progenitor numbers were also increased by an order of magnitude when mAb HP1/2 was given after 5 d of granulocyte colony-stimulating factor treatment (64). The data provide evidence for a role for $\alpha 4$ integrins in progenitor cell function and trafficking in vivo and may provide a novel clinical application for $\alpha 4$ integrin blockade, since the use of peripheralized stem and progenitor cells for autologous transplantation after chemotherapy and for gene therapy applications is becoming of increasing importance in clinical medicine (84).

Intervention in vivo with alternative antagonists

Although mAbs blocking the in vitro function of VCAM1 in mouse, rat, rabbit, and cynomolgus monkey have been described, their use in vivo to probe the role of VCAM1 has been limited. The use of mAbs to VCAM1 in murine EAE, diabetes, and lung recruitment was described earlier, and these mAbs have also been used in allograft rejection studies (85). A recent study also showed that F(ab')2 fragments of an mAb to VCAM1 significantly inhibited $CD2^+$ lymphocyte accumulation in response to tuberculin in a primate DTH response (86). The data so far suggest that VCAM1 indeed can play a role in leukocyte recruitment, as originally hypothesized (65, 87). Although absence of VCAM1 by immunohistology has often been used to infer lack of importance in pathology, it is in fact unclear whether VCAM1 is really absent from normal vessels or merely present at levels below detection by standard immunohistochemical methods. Interestingly, mAbs to VCAM1 were found to block monocyte transendothelial migration in vitro, despite undetectable levels of VCAM1 on human umbilical vein endothelial cells when examined by mAb staining (47). Since VCAM1 clearly can mediate signal transduction (see above), low levels may be sufficient to promote a migratory phenotype (42) in the absence of strong adhesion. The availability and wider in vivo exploitation of VCAM1-directed mAbs should help clarify these points.

Blocking mAbs to murine MadCAM and to both the murine $\beta 7$ chain and the $\alpha 4\beta 7$ complex are now available and should prove to be valuable reagents to dissect the role of alternative pathways in this species, as shown in recent elegant studies on gut lymphocyte homing (77).

Finally, Fn-derived peptides have shown efficacy in murine contact hypersensitivity and rat adjuvant arthritis models, as well as in tranforming growth factor-$\beta 1$ knockout mice (88–90). The mechanism of action of these peptides in these models remains undefined, although they are presumed to interact with and block VLA4, VLA5, or $\alpha 4\beta 7$.

Side effects of mAbs to $\alpha 4$

The in vivo studies published to date have been concerned with the demonstration of therapeutic efficacy, and, not surprisingly, little attention has been paid so far to possible side effects of $\alpha 4$ integrin blockade. Nevertheless, $\alpha 4$-dependent adhesion pathways must play physiologic roles in leukocyte biology, and, therefore, blockade of these pathways will presumably have deleterious effects on normal immune and inflammatory responses. Blockade of this integrin does not block acute PMN emigration (see above), and, therefore, $\alpha 4$ integrin blockade should not affect acute PMN-dependent clearance of infectious organisms. However, a recent publication shows that $\alpha 4$ mAbs can have deleterious effects on clearance of infectious organisms in the gut (91). Rats treated with mAb TA-2 are unable to effectively resolve intestinal nematode infections, which are cleared by T cell–dependent mechanisms, arguing that $\alpha 4$ integrins play a central role in several areas of lymphocyte-dependent intestinal immunity (91). Recent studies also show that intestinal invasion of mice with the bacterium *Yersinia enterocolitica*, which is also cleared by T cell–dependent mechanisms, is significantly enhanced in the presence of $\alpha 4$-directed mAbs (Autenreith, I., personal communication).

Other possible mechanism-based side effects, based on tissue distribution of VCAM1 and $\alpha 4$ integrins, might include effects on antibody formation, hematopoiesis, neural development, mucosal immunity, muscle development, and wound healing, and it is clear that the side effects of $\alpha 4$ integrin blockade require further study.

Mechanism of action of $\alpha 4$ mAbs in vivo

Although blockade of recruitment into tissues clearly occurs in vivo and provides an explanation for the disease-modifying effects of mAbs in certain models, it is also apparent that mAbs can block disease in the absence of recruitment blockade. The

most striking example of this is in the sheep model of allergic AHR, where mAb HP1/2 is effective as an aerosol (62). These observations raise important issues about the mechanism of action of these mAbs, which have all been selected on the basis of blockade of adhesive function in vitro. In fact, $\alpha 4$ integrin–dependent adhesion is likely crucial not only to recruitment but also to leukocyte function within tissues. Adhesion-dependent enhancement of leukocyte function is well established in vitro for the $\beta 2$ integrins, and recent studies show the same phenomenon for $\alpha 4$ integrins on both eosinophils and T cells (42, 92). Recent studies also show that eosinophil activation state rather than number is critical to increased AHR in vivo in the guinea pig (93). Therefore, inhibition of adhesion-dependent priming and/or activation of leukocytes, either during transendothelial migration or when within tissues, provides an explanation for mAb efficacy despite lack of inhibition of recruitment.

It is also clear that mAbs to $\alpha 4$ integrins can trigger or prime leukocytes in vitro, for example to release cytokines (43), which are known to modulate disease. For example, TNF will delay the onset of diabetes in NOD mice (75), and induction of monocyte TNF release by mAbs crosslinking $\alpha 4$ could provide an alternative rationale for efficacy observed in the NOD model (74–76). In addition, the effector functions of mAbs can play an important role in their in vivo efficacy profiles. Several approaches can be taken to address these issues. First, IgG fragments lacking effector function can be tested. Of most value are monovalent Fab fragments which cannot crosslink receptors. In fact, monovalent Fab fragments of HP1/2 show comparable efficacy with HP1/2 IgG in vivo in blocking sheep LPR and AHR (94). Second, isotype-matched nonblocking mAbs can be used as effective controls. For example, mAb B5G10, an $\alpha 4$ mAb which is the same isotype as mAb HP1/2 and which binds primate $\alpha 4$ but does not block adhesive function, does not peripheralize progenitor cells in baboon studies (Papayannopoulou, T., and R. R. Lobb, unpublished data). Third, mAb HP1/2 does not induce cytokine RNA expression in human monocytes in vitro (Haskill, S., L. Osborn, and R. R. Lobb, unpublished data). These results are all consistent with mAb HP1/2 working in vivo by blockade of $\alpha 4$ integrin–dependent adhesive function. In the mouse system, Fab fragments of PS/2 have been examined and still block $\alpha 4$-dependent function (77). Finally, the equal efficacy of VCAM1-directed and $\alpha 4$-directed mAbs in two murine models argues that blockade of adhesion is the mechanism of action in these cases. In conclusion, the data from several in vivo studies argue for a mechanism of blockade of adhesion-dependent function, but further examination of these issues will be of value.

Summary

In this review we have summarized the rapidly mounting evidence for a central role for the integrins VLA4 and $\alpha 4\beta 7$ in leukocyte pathophysiology. Five distinct $\alpha 4$ mAbs, each able to block $\alpha 4$-dependent adhesion in vitro, show beneficial effects in vivo in seven different species (mouse, rat, guinea pig, rabbit, sheep, and New-World and Old-World monkeys) and in a wide variety of organ systems, including colon, lung, skin, neural tissue, pancreas, peritoneum, and the vessel wall (Table I). A number of important issues remain to be addressed, including the relative importance of VLA4 and $\alpha 4\beta 7$ and of their counterligands VCAM1, Fn, and MadCAM, in most in vivo settings; alternative mechanisms for mAb efficacy other than adhesion blockade; poor understanding of side effects of $\alpha 4$ blockade; and the role of integrin signaling rather than adhesion in function. Nevertheless, the data argue that $\alpha 4$ integrins will likely play critical roles in both normal physiology and pathology in man. To examine this issue, a humanized IgG4 isotype of mAb HP1/2 has been generated which retains full in vitro potency and in vivo efficacy (Lobb, R., D. Leone, B. Pepinsky, P. Tempest, F. Carr, W. Abraham, and S. Nourshargh, unpublished data). This mAb will enter clinical trials in the near future to extend in vivo studies to humans and to identify clinical areas of value. This area of leukocyte adhesion biology promises to remain a fruitful area of research and should continue to provide critical clues as to intervention points in human disease.

Note added in proof. Since submission of this manuscript, an excellent review of endothelial-leukocyte adhesion has been published (96). In addition, we omitted a paper showing that treatment of mice with mAbs to either VLA-4 or VCAM-1 both prolonged cardiac allograft survival and greatly suppressed antibody titer to human gammaglobulin (97).

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References

1. Hemler, M. E., M. J. Elices, C. Parker, and Y. Takada. 1990. Structure of the integrin VLA-4 and its cell-cell and cell-matrix adhesion functions. *Immunol. Rev.* 114:45–60.

2. Bevilacqua, M. P. 1993. Endothelial-leukocyte adhesion molecules. *Annu. Rev. Immunol.* 11:767–804.

3. Postigo, A. A., J. Teixido, and F. Sanchez-Madrid. 1993. The $\alpha 4\beta 1$/VCAM-1 adhesion pathway in physiology and disease. *Res. Immunol.* 144:723–735.

4. Springer, T. A. 1994. Traffic signals for lymphocyte recirculation and leukocyte emigration: the multistep paradigm. *Cell.* 76:301–314.

5. Holzmann, B., B. W. McIntyre, and I. L. Weissman. 1989. Identification of a murine Peyer's patch: specific lymphocyte homing receptor as an integrin molecule with an α chain homologous to human VLA-4 α. *Cell.* 56:37–46.

6. Berlin, C., E. L. Berg, M. J. Briskin, D. P. Andrew, P. J. Kilshaw, B. Holzmann, I. L. Weissman, A. Hamann, and E. C. Butcher. 1993. $\alpha 4\beta 7$ integrin mediates lymphocyte binding to the mucosal vascular addressin MAdCAM-1. *Cell.* 74:185–195.

7. Chan, B. M., M. J. Elices, E. Murphy, and M. E. Hemler. 1992. Adhesion to vascular cell adhesion molecule 1 and fibronectin. Comparison of $\alpha 4\beta 1$ (VLA-4) and $\alpha 4\beta 7$ on the human B cell line JY. *J. Biol. Chem.* 267:8366–8370.

8. Ruegg, C., A. A. Postigo, E. E. Sikorski, E. C. Butcher, R. Pytela, and D. J. Erle. 1992. Role of integrin $\alpha 4\beta 7/\alpha 4\beta P$ in lymphocyte adherence to fibronectin and VCAM-1 and in homotypic cell clustering. *J. Cell Biol.* 117:179–189.

9. Bochner, B. S., F. W. Luscinskas, M. A. Gimbrone, Jr., W. Newman, S. A. Sterbinsky, C. P. Derse-Anthony, D. Klunk, and R. P. Schleimer. 1991. Adhesion of human basophils, eosinophils, and neutrophils to interleukin 1–activated human vascular endothelial cells: contributions of endothelial cell adhesion molecules. *J. Exp. Med.* 173:1553–1556.

10. Kilshaw, P. J., and S. J. Murant. 1990. A new surface antigen on intraepithelial lymphocytes in the intestine. *Eur. J. Immunol.* 20:2201–2207.

11. Schweighoffer, T., Y. Tanaka, M. Tidswell, D. J. Erle, K. J. Horgan, G. E. Luce, A. I. Lazarovits, D. Buck, and S. Shaw. 1993. Selective expression of integrin $\alpha 4\beta 7$ on a subset of human $CD4^+$ memory T cells with hallmarks of gut-trophism. *J. Immunol.* 151:717–729.

12. Lazarovits, A. I., and J. Karsh. 1993. Differential expression in rheumatoid synovium and synovial fluid of $\alpha 4\beta 7$ integrin. *J. Immunol.* 151:6482–6489.

13. Erle, D. J., M. J. Briskin, E. C. Butcher, A. Garcia-Pardo, A. I. Lazarovits, and M. Tidswell. 1994. Expression and function of the MadCAM-1 receptor, integrin $\alpha 4\beta 7$, on human leukocytes. *J. Immunol.* 153:517–528.

14. Rosen, G. D., J. R. Sanes, R. LaChance, J. M. Cunningham, J. Roman,

and D. C. Dean. 1992. Roles for the integrin VLA-4 and its counter receptor VCAM-1 in myogenesis. *Cell.* 69:1107–1119.

15. Sheppard, A. M., M. D. Onken, G. D. Rosen, P. G. Noakes, and D. C. Dean. 1994. Expanding roles for α4 integrin and its ligands in development. *Cell Adhesion and Communication* 2:27–43.

16. Komoriya, A., L. J. Green, M. Mervic, S. S. Yamada, K. M. Yamada, and M. J. Humphries. 1991. The minimal essential sequence for a major cell-type specific adhesion site (CS1) within the alternatively spliced type III connecting segment domain of fibronectin is leucine-aspartic acid-valine. *J. Biol. Chem.* 266:15075–15079.

17. Osborn, L., C. Vassallo, and C. D. Benjamin. 1992. Activated endothelium binds lymphocytes through a novel binding site in the alternately spliced domain of vascular cell adhesion molecule-1. *J. Exp. Med.* 176:99–107.

18. Vonderheide, R. H., and T. A. Springer. 1992. Lymphocyte adhesion through very late antigen 4: evidence for a novel binding site in the alternatively spliced domain of vascular cell adhesion molecule 1 and an additional α4 integrin counter-receptor on stimulated endothelium. *J. Exp. Med.* 175:1433–1442.

19. Vonderheide, R. H., T. F. Tedder, T. A. Springer, and D. E. Staunton. 1994. Residues within a conserved amino acid motif of domains 1 and 4 of VCAM-1 are required for binding to VLA-4. *J. Cell Biol.* 125:215–222.

20. Osborn, L., C. Vassallo, B. G. Browning, R. Tizard, D. O. Haskard, C. D. Benjamin, I. Dougas, and T. Kirchhausen. 1994. Arrangement of domains, and amino acid residues required for binding of vascular cell adhesion molecule-1 to its counter receptor VLA-4 ($\alpha_4\beta_1$). *J. Cell Biol.* 124:601–608.

21. Pulido, R., M. J. Elices, M. R. Campanero, L. Osborn, S. Schiffer, A. Garcia-Pardo, R. Lobb, M. E. Hemler, and F. Sanchez-Madrid. 1991. Functional evidence for three distinct and independently inhibitable adhesion activities mediated by the human integrin VLA-4. Correlation with distinct α4 epitopes. *J. Biol. Chem.* 266:10241–10245.

22. Makarem, R., P. Newham, J. A. Askari, L. J. Green, J. Clements, M. Edwards, M. J. Humphries, and A. P. Mould. 1994. Competitive binding of vascular cell adhesion molecule-1 and the HepII/IIICS domain of fibronectin to the integrin α4β1. *J. Biol. Chem.* 269:4005–4011.

23. Masumoto, A., and M. E. Hemler. 1993. Multiple activation states of VLA-4. Mechanistic differences between adhesion to CS1/fibronectin and to vascular cell adhesion molecule-1. *J. Biol. Chem.* 268:228–234.

24. Pulido, R., M. R. Campanero, A. Garcia-Pardo, and F. Sanchez-Madrid. 1991. Structure-function analysis of the human integrin VLA-4 (α4β1). Correlation of proteolytic α4 peptides with α4 epitopes and sites of ligand interaction. *FEBS (Fed. Eur. Biochem. Soc.) Lett.* 294:121–124.

25. Iida, J., A. P. N. Skubitz, L. T. Furcht, E. A. Wayner, and J. B. McCarthy. 1992. Coordinate role for cell surface chondroitin sulfate proteoglycan and α4β1 integrin in mediating melanoma cell adhesion to fibronectin. *J. Cell Biol.* 118:431–444.

26. Mould, A. P., A. Komoriya, K. M. Yamada, and M. J. Humphries. 1991. The CS5 peptide is a second site in the IIICS region of fibronectin recognized by the integrin α4β1. Inhibition of α4β1 function by RGD peptide homologues. *J. Biol. Chem.* 266:3579–3585.

27. Sanchez-Aparicio, P., C. Dominguez-Jimenez, and A. Garcia-Pardo. 1994. Activation of the α4β1 integrin through the β1 subunit induces recognition of the RGDS sequence in fibronectin. *J. Cell Biol.* 126:271–279.

28. Yabkowitz, R., V. M. Dixit, N. Guo, D. D. Roberts, and Y. Shimizu. 1993. Activated T cell adhesion to thrombospondin is mediated by the α4β1 (VLA-4) and α5β1 (VLA-5) integrins. *J. Immunol.* 151:149–158.

29. Isberg, R. R., and J. M. Leong. 1990. Multiple β1 chain integrins are receptors for invasin, a protein that promotes bacterial penetration into mammalian cells. *Cell.* 60:861–871.

30. Shimizu, Y., G. A. Van Seventer, K. J. Horgan, and S. Shaw. 1990. Regulated expression and binding of three VLA (β1) integrin receptors on T cells. *Nature (Lond.).* 345:250–253.

31. Tanaka, Y., D. H. Adams, S. Hubscher, H. Hirano, U. Siebenlist, and S. Shaw. 1993. T-cell adhesion induced by proteoglycan-immobilized cytokine MIP-1β. *Nature (Lond.).* 361:79–82.

32. Honda, S., J. J. Campbell, D. P. Andrew, B. Engelhardt, B. A. Butcher, R. A. Warnock, R. D. Ye, and E. C. Butcher. 1994. Ligand-induced adhesion to activated endothelium and to vascular cell adhesion molecule-1 in lymphocytes transfected with the *N*-formyl peptide receptor. *J. Immunol.* 152:4026–4035.

33. Carlos, T. M., B. R. Schwartz, N. L. Kovach, E. Yee, M. Rosa, L. Osborn, G. Chi-Rosso, R. Lobb, and J. M. Harlan. 1990. Vascular cell adhesion molecule-1 mediates lymphocyte adherence to cytokine-activated cultured human endothelial cells. *Blood.* 76:965–970.

34. Masumoto, A., and M. E. Hemler. 1993. Mutation of putative divalent cation sites in the α^4 subunit of the integrin VLA-4: distinct effects on adhesion to CS1/fibronectin, VCAM-1, and invasin. *J. Cell Biol.* 123:245–253.

35. Kassner, P. D., and M. E. Hemler. 1993. Interchangeable α chain cytoplasmic domains play a positive role in control of cell adhesion mediated by VLA-4, a β_1 integrin. *J. Exp. Med.* 178:649–660.

36. Kassner, P. D., S. Kawaguchi, and M. E. Hemler. 1994. Minimum α chain sequence needed to support integrin-mediated adhesion. *J. Biol. Chem.* 269:19859–19867.

37. Crowe, D. T., H. Chiu, S. Fong, and I. L. Weissman. 1994. Regulation of the avidity of integrin α4β7 by the β7 cytoplasmic domain. *J. Biol. Chem.* 269:14411–14418.

38. Nojima, Y., M. J. Humphries, A. P. Mould, A. Komoriya, K. M. Yamada, S. F. Schlossman, and C. Morimoto. 1990. VLA-4 mediates CD3-dependent CD4$^+$ T cell activation via the CS1 alternatively spliced domain of fibronectin. *J. Exp. Med.* 172:1185–1192.

39. Burkly, L. C., A. Jakubowski, B. M. Newman, M. D. Rosa, G. Chi-Rosso, and R. R. Lobb. 1991. Signaling by vascular cell adhesion molecule-1 (VCAM-1) through VLA-4 promotes CD3-dependent T cell proliferation. *Eur. J. Immunol.* 21:2871–2875.

40. Damle, N. K., K. Klussman, G. Leytze, A. Aruffo, P. S. Linsley, and J. A. Ledbetter. 1993. Costimulation with integrin ligands intercellular adhesion molecule-1 or vascular cell adhesion molecule-1 augments activation-induced death of antigen-specific CD4$^+$ T lymphocytes. *J. Immunol.* 151:2368–2379.

41. Koopman, G., R. M. J. Keehnen, E. Lindhout, W. Newman, Y. Shimizu, G. A. Van Seventer, C. de Groot, and S. T. Pals. 1994. Adhesion through LFA-1 (CD11a/CD18)-ICAM-1 (CD54) and the VLA-4 (CD49d)-VCAM-1 (CD106) pathways prevents apoptosis of germinal center B cells. *J. Immunol.* 152:3760–3767.

42. Romanic, A. M., and J. A. Madri. 1994. The induction of 72-kD gelatinase in T cells upon adhesion to endothelial cells is VCAM-1 dependent. *J. Cell Biol.* 125:1165–1178.

43. Yurochko, A. D., D. Y. Liu, D. Eierman, and S. Haskill. 1992. Integrins as a primary signal transduction molecule regulating monocyte immediate-early gene induction. *Proc. Natl. Acad. Sci. USA* 89:9034–9038.

44. Nojima, Y., D. M. Rothstein, K. Sugita, S. F. Schlossman, and C. Morimoto. 1992. Ligation of VLA-4 on T cells stimulates tyrosine phosphorylation of a 105-kD protein. *J. Exp. Med.* 175:1045–1053.

45. Freedman, A. S., K. Rhynhart, Y. Nojima, J. Svahn, L. Eliseo, C. D. Benjamin, C. Morimoto, and E. Vivier. 1993. Stimulation of protein tyrosine phosphorylation in human B cells after ligation of the β1 integrin VLA-4. *J. Immunol.* 150:1645–1652.

46. Chuluyan, H. E., and A. C. Issekutz. 1993. VLA-4 integrin can mediate CD11/CD18-independent transendothelial migration of human monocytes. *J. Clin. Invest.* 92:2768–2777.

47. Meerschaert, J., and M. B. Furie. 1994. Monocytes use either CD11/CD18 or VLA-4 to migrate across human endothelium in vitro. *J. Immunol.* 152:1915–1926.

48. Chan, P.-Y., and A. Aruffo. 1993. VLA-4 integrin mediates lymphocyte migration on the inducible endothelial cell ligand VCAM-1 and the extracellular matrix ligand fibronectin. *J. Biol. Chem.* 268:24655–24664.

49. Miyake, K., Y. Hasunuma, H. Yagita, and M. Kimoto. 1992. Requirement for VLA-4 and VLA-5 integrins in lymphoma cell binding to and migration beneath stromal cells in culture. *J. Cell Biol.* 119:653–662.

50. Chan, B. M. C., P. D. Kassner, J. A. Schiro, H. R. Byers, T. S. Kupper, and M. E. Hemler. 1992. Distinct cellular functions mediated by different VLA integrin α subunit cytoplasmic domains. *Cell.* 68:1051–1060.

51. Takada, Y., M. J. Elices, C. Crouse, and M. E. Hemler. 1989. The primary structure of the α4 subunit of VLA-4: homology to other integrins and a possible cell-cell adhesion function. *EMBO (Eur. Mol. Biol. Organ.) J.* 8:1361–1368.

52. Neuhaus, H., M. C.-T. Hu, M. E. Hemler, Y. Takada, B. Holzmann, and I. L. Weissman. 1991. Cloning and expression of cDNAs for the α subunit of the murine lymphocyte Peyer's patch homing receptor. *J. Cell Biol.* 115:1149–1158.

53. Palmer, E. L., C. Rüegg, R. Ferrando, R. Pytela, and D. Sheppard. 1993. Sequence and tissue distribution of the integrin α9 subunit, a novel partner of β1 that is widely distributed in epithelia and muscle. *J. Cell Biol.* 123:1289–1297.

54. Teixido, J., C. M. Parker, P. D. Kassner, and M. E. Hemler. 1992. Functional and structural analysis of VLA-4 integrin α4 subunit cleavage. *J. Biol. Chem.* 267:1786–1791.

55. Parker, C. M., C. Pujades, M. B. Brenner, and M. E. Hemler. 1993. α4/180: a novel form of the integrin α4 subunit. *J. Biol. Chem.* 268:7028–7035.

56. Bednarczyk, J. L., M. C. Szabo, J. N. Wygant, A. I. Lazarovits, and B. W. McIntyre. 1994. Identification of a combinatorial epitope expressed by the integrin α4β1 heterodimer involved in the regulation of cell adhesion. *J. Biol. Chem.* 269:8348–8354.

57. Miyake, K., I. L. Weissman, J. S. Greenberger, and P. W. Kincade. 1991. Evidence for a role of the integrin VLA-4 in hemopoeisis. *J. Exp. Med.* 173:599–607.

58. Issekutz, T. B. 1991. Inhibition of in vivo lymphocyte migration to inflammation and homing to lymphoid tissues by the TA-2 monoclonal antibody. A likely role for VLA-4 in vivo. *J. Immunol.* 147:4178–4184.

59. Yednock, T. A., C. Cannon, L. C. Fritz, F. Sanchez-Madrid, L. Steinman, and N. Karin. 1992. Prevention of experimental autoimmune encephalomyelitis by antibodies against α4β1 integrin. *Nature (Lond.).* 356:63–66.

60. Weg, V. B., T. J. Williams, R. R. Lobb, and S. Nourshargh. 1993. A monoclonal antibody recognizing very late activation antigen-4 inhibits eosinophil accumulation in vivo. *J. Exp. Med.* 177:561–566.

61. Winn, R. K., and J. M. Harlan. 1993. CD18-independent neutrophil and

mononuclear leukocyte emigration into the peritoneum of rabbits. *J. Clin. Invest.* 92:1168–1173.

62. Abraham, W. M., M. W. Sielczak, A. Ahmed, A. Cortes, I. T. Lauredo, J. Kim, B. Pepinsky, C. D. Benjamin, D. R. Leone, R. R. Lobb, and P. F. Weller. 1994. α_4-Integrins mediate antigen-induced late bronchial responses and prolonged airway hyperresponsiveness in sheep. *J. Clin. Invest.* 93:776–787.

63. Podolsky, D. K., R. Lobb, N. King, C. D. Benjamin, B. Pepinsky, P. Sehgal, and M. deBeaumont. 1993. Attenuation of colitis in the Cotton-top tamarin by anti-α4 integrin monoclonal antibody. *J. Clin. Invest.* 92:372–380.

64. Papayannopoulou, T., and B. Nakamoto. 1993. Peripheralization of hematopoietic progenitors in primates treated with anti-VLA4 integrin. *Proc. Natl. Acad. Sci. USA.* 90:9374–9378.

65. Elices, M. J., L. Osborn, Y. Takada, C. Crouse, S. Luhowskyj, M. E. Hemler, and R. R. Lobb. 1990. VCAM-1 on activated endothelium interacts with the leukocyte integrin VLA-4 at a site distinct from the VLA-4/fibronectin binding site. *Cell.* 60:577–584.

66. Issekutz, T. B., and A. C. Issekutz. 1991. T lymphocyte migration to arthritic joints and dermal inflammation in the rat: differing migration patterns and the involvement of VLA-4. *Clin. Immunol. Immunopathol.* 61:436–447.

67. Baron, J. L., J. A. Madri, N. H. Ruddle, G. Hashim, and C. A. Janeway, Jr. 1993. Surface expression of α4 integrin by CD4 T cells is required for their entry into brain parenchyma. *J. Exp. Med.* 177:57–68.

68. Issekutz, T. B. 1993. Dual inhibition of VLA-4 and LFA-1 maximally inhibits cutaneous delayed-type hypersensitivity. *Am. J. Pathol.* 143:1286–1293.

69. Mulligan, M. S., C. W. Swith, D. C. Anderson, R. F. Todd III, M. Miyasaka, T. Tamatani, T. B. Issekutz, and P. Ward. 1993. Role of leukocyte adhesion molecules in complement-induced lung injury. *J. Immunol.* 159:2401–2406.

70. Paul, L. C., A. Davidoff, H. Benediktsson, and T. B. Issekutz. 1993. The efficacy of LFA-1 and VLA-4 antibody treatment in rat vascularized cardiac allograft rejection. *Transplantation (Baltimore).* 55:1196–1199.

71. Nakajima, H., H. Sano, T. Nishimura, S. Yoshida, and I. Iwamoto. 1994. Role of vascular cell adhesion molecule 1/very late activation antigen 4 and intercellular adhesion molecule 1/lymphocyte function–associated antigen 1 interactions in antigen-induced eosinophil and T cell recruitment into the tissue. *J. Exp. Med.* 179:1145–1154.

72. Ferguson, T. A., and T. S. Kupper. 1993. Antigen-independent processes in antigen-specific immunity. *J. Immunol.* 150:1172–1182.

73. Chisholm, P. L., C. A. Williams, and R. R. Lobb. 1993. Monoclonal antibodies to the integrin α-4 subunit inhibit the murine contact hypersensitivity response. *Eur. J. Immunol.* 23:682–688.

74. Yang, X.-D., N. Karin, R. Tisch, L. Steinman, and H. O. McDevitt. 1993. Inhibition of insulitis and prevention of diabetes in nonobese diabetic mice by blocking L-selectin and very late antigen-4 adhesion receptors. *Proc. Natl. Acad. Sci. USA.* 90:10494–10498.

75. Burkly, L. C., A. Jakubowski, and M. Hattori. 1994. Protection against adoptive transfer of autoimmune diseases mediated through very late antigen-4 integrin. *Diabetes.* 43:529–534.

76. Baron, J. L., E.-P. Reich, I. Visintin, and C. A. Janeway, Jr. 1994. The pathogenesis of adoptive murine autoimmune diabetes requires an interaction between α4-integrins and vascular cell adhesion molecule-1. *J. Clin. Invest.* 93:1700–1708.

77. Hamann, A., D. P. Andrew, D. Jablonski-Westrich, B. Holzmann, and E. C. Butcher. 1994. The role of α4-integrins in lymphocyte homing to mucosal tissues in vivo. *J. Immunol.* 152:3282–3293.

78. Mulligan, M. S., G. P. Wilson, R. F. Todd III, C. W. Swith, D. C. Anderson, J. Varani, T. B. Issekutz, M. Miyasaka, T. Tamatani, J. R. Ruche, et al. 1993. Role of β1, β2 integrins and ICAM1 in lung injury after deposition of IgG and IgA immune complexes. *J. Immunol.* 159:2407–2417.

79. Mulligan, M. S., K. J. Johnson, R. F. Todd III, T. B. Issekutz, M. Miyasaka, T. Tamatani, C. W. Swith, D. C. Anderson, and P. A. Ward. 1993. Requirements for leukocyte adhesion molecules in nephrotoxic nephritis. *J. Clin. Invest.* 91:577–587.

80. Molina, A., F. Sanchez-Madrid, T. Bricio, A. Martin, A. Barat, V. Alvarez, and F. Mampaso. 1994. Prevention of mercuric chloride-induced nephritis in the Brown Norway rat by treatment with antibodies against the α4 integrin. *J. Immunol.* 153:2313–2320.

81. Rabb, H. A., R. Olivenstein, T. B. Issekutz, P. M. Renzi, J. G. Martin, R. Pantano, and S. Seguin. 1994. The role of the leukocyte adhesion molecules VLA4, LFA1, and Mac1 in allergic airway responses in the rat. *Am. J. Respir. Crit. Care Med.* 149:1186–1191.

82. Pretolani, M., C. Ruffie, J.-R. Lapa e Silva, D. Joseph, R. R. Lobb, and B. Vargaftig. 1994. Antibody against very late antigen-4 prevents antigen-induced bronchial hyperreactivity and cellular infiltration in guinea-pig airways. *J. Exp. Med.* 180:795–805.

83. Milne, A. A. Y., and P. J. Piper. 1994. The role of VLA-4 integrin in the recruitment of leukocytes and development of bronchial hyperresponsiveness in the guinea-pig. *Br. J. Pharmacol.* 112:82Pa.(Abstr.)

84. Kessinger, A., and J. O. Armitage. 1991. The evolving role of autologous peripheral stem cell transplantation in cancer patients following high-dose chemotherapy for malignancies. *Blood.* 77:211–213.

85. Orosz, C. G., A. van Buskirk, D. D. Sedmak, P. Kincade, K. Miyake, and R. P. Pelletier. 1992. Role of the endothelial adhesion molecule VCAM in murine cardiac allograft rejection. *Immunol. Lett.* 32:7–12.

86. Silber, A., W. Newman, V. G. Sasseville, D. Pauley, D. Beall, D. G. Walsh, and D. J. Ringler. 1994. Recruitment of lymphocytes during cutaneous delayed hypersensitivity in nonhuman primates is dependent on E-selectin and vascular cell adhesion molecule 1. *J. Clin. Invest.* 93:1554–1563.

87. Osborn, L., C. Hession, R. Tizard, C. Vassallo, S. Luhowskyj, G. Chi-Rosso, and R. Lobb. 1989. Direct expression cloning of vascular cell adhesion molecule 1, a cytokine-induced endothelial protein that binds to lymphocytes. *Cell.* 59:1203–1211.

88. Ferguson, T. A., H. Mizutani, and T. S. Kupper. 1991. Two integrin-binding peptides abrogate T cell–mediated immune responses in vivo. *Proc. Natl. Acad. Sci. USA.* 88:8072–8076.

89. Hines, K. L., A. B. Kulkarni, J. B. McCarthy, H. Tian, J. M. Ward, M. Christ, N. L. McCartney-Francis, L. T. Furcht, S. Karlsson, and S. Wahl. 1994. Synthetic fibronectin peptides interrupt inflammatory cell infiltration in transforming growth factor β1 knockout mice. *Proc. Natl. Acad. Sci. USA.* 91:5187–5191.

90. Wahl, S. M., J. B. Allen, K. L. Hines, T. Imamichi, A. M. Wahl, L. T. Furcht, and J. B. McCarthy. 1994. Synthetic fibronectin peptides suppress arthritis in rats by interrupting leukocyte adhesion and recruitment. *J. Clin. Invest.* 94:655–662.

91. Bell, R. G., and T. B. Issekutz. 1993. Expression of a protective intestinal immune response can be inhibited at three distinct sites by treatment with anti-α4 integrin. *J. Immunol.* 151:4790–4802.

92. Anwar, A. R. F., R. Moqbel, G. M. Walsh, A. B. Kay, and A. J. Wardlaw. 1993. Adhesion to fibronectin prolongs eosinophil survival. *J. Exp. Med.* 177:839–843.

93. Pretolani, M., C. Ruffie, D. Joseph, M. G. Campos, M. K. Church, J. Lefort, and B. Vargaftig. 1994. Role of eosinophil activation in the bronchial reactivity of allergic guinea-pigs. *Am. J. Respir. Crit. Care Med.* 149:1167–1174.

94. Lobb, R. R., B. Pepinsky, D. R. Leone, and W. M. Abraham. 1995. The role of α4 integrins in lung pathophysiology. *Eur. Respir. J.* In press.

95. Sadahiro, M., T. O. McDonald, and M. D. Allen. 1993. Reduction in cellular and vascular rejection by blocking leukocyte adhesion molecule receptors. *Am. J. Pathol.* 142:675–683.

96. Carlos, T. M., and J. M. Harlan. 1994. Leukocyte-endothelial adhesion molecules. *Blood.* 84:2068–2101.

97. Isobe, M., J. Suzuki, H. Yagita, K. Okumura, and M. Sekiguchi. 1994. Effect of anti-VCAM-1 and anti-VLA-4 monoclonal antibodies on cardiac allograft survival and response to soluble antigens in mice. *Transplant. Proc.* 26:867–868.

Asthma

Asthma Basics

SEARCH

What is Asthma?

In many people, asthma appears to be an allergic reaction to substances commonly breathed in through the air, such as animal dander, pollen, or dust mite and cockroach waste products. The catch-all name for these substances, allergens, refers to anything that provokes an allergic reaction. Some people have a genetic predisposition to react to certain allergens.

When these people breathe in the allergen, the immune system goes into high gear as if fighting off a harmful parasite. The system produces a molecule called immunoglobulin E (IgE), one of a class of defensive molecules termed antibodies. The IgE antibody is central to the allergic reaction. For example, it causes mast cells, a type of specialized defensive cell, to release chemical "weapons" into the airways. The airways then become inflamed and constricted, leading to coughing, wheezing, and difficulty breathing -- an asthma attack.

Without treatment, such as inhaled corticosteriods to reduce the inflammation, asthma attacks can be deadly. The overall death rate for asthma, however, is low.

Why is Asthma on the Rise?

Although several theories exist about why asthma rates have risen during the last two decades, there probably is no simple answer, says Calman Prussin, M.D., head of the clinical allergy and immunology unit at NIAID.

One theory is that people today, especially in developed countries, are spending more time indoors, Dr. Prussin says. We are therefore exposed to more indoor allergens, such as dust mite allergen, that cause asthma. "Our houses are now hermetically sealed to save heating and cooling energy," he notes, "and unfortunately this causes more indoor allergen exposure."

Another reason may be that people today live in cleaner, more sanitary conditions than they did before the industrial revolution, relatively free of disease-causing viruses and bacteria, he says. This clean living affects our immune system. The immune system's defensive white blood cells, called T cells, have two basic "settings," he explains. Th1 cells fight infectious viruses and bacteria. Th2 cells fight parasites but are also involved in allergic reactions.

"We are exposed to fewer viruses and bacteria than people were 100 years ago, so perhaps our immune systems have not learned to make Th1 cells as well," Dr. Prussin says. "That means we have a greater proportion of Th2 cells in our bodies, which might lead to more allergies and asthma."

Other theories point to increased levels of air pollutants, a decline in the amount of

exercise people get, or rising obesity as factors in the increase of asthma.

Asthma Statistics

1. In 1998, an estimated 17 million Americans, or 6.4 percent of the population, had asthma. Children account for 4.8 million of Americans with asthma.

2. Asthma affects slightly more African Americans (5.8 percent) than whites (5.1 percent). In 1993 however, African Americans were 3 to 4 times more likely than whites to be hospitalized for asthma. In 1996, African Americans were 4 to 6 times more likely than whites to die from asthma.

3. More than 5,000 people die from asthma each year in the United States. Although asthma deaths are infrequent, they have increased significantly during the last two decades. From 1975-1979, the death rate was 8.2 per 100,000 people. That rate jumped in 1993-1995 to 17.9 per 100,000.

4. In 1994, asthma caused 451,000 hospitalizations. Children under 15 accounted for 169,000 of these.

5. In 1995, asthma caused more than 1.8 million emergency room visits.

6. Asthma cost the U.S. economy an estimated $10.7 billion in 1994, including a direct health care cost of $6.1 billion and indirect costs, such as lost work days, of $4.6 billion.

References

1. Centers for Disease Control and Prevention (CDC), *Morbidity and Mortality Weekly Report* 47(47):1022-25 (December 4, 1998).

2. C. Cannon *et al. American Journal of Respiratory and Critical Care Medicine* 158 (1): 320-34 (1998).

3. CDC Surveillance Summaries, April 24, 1998, from *Morbidity and Mortality Weekly Report* 47(SS-1): 1-28 (1998).

4. CDC, *Morbidity and Mortality Weekly Report* 45(17): 350-3 (1996).

5. K.B. Weiss *et al.* *Journal of the American Medical Association* 264(13):1683-7 (1990).

6. CDC, National Center for Health Statistics, *National Vital Statistics Report* 47(4) (1997).

7. CDC Surveillance Summaries, April 24, 1998, from *Morbidity and Mortality Weekly Report* 47(SS-1): 1-28 (1998).

8. National Center for Health Statistics, National Health Interview Survey, 1994.

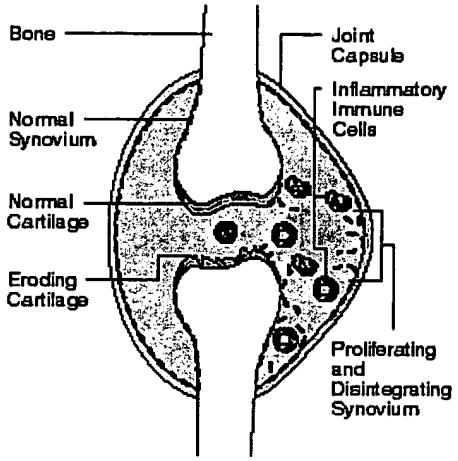
9. CDC Surveillance Summaries, April 24, 1998, from *Morbidity and Mortality Weekly Report* 47(SS-1): 1-28 (1998).

10. K.B. Weiss *et al.* *Journal of Allergy and Clinical Immunology* 106(3): 493-99 (2000).

What Are Some Examples of Autoimmune Diseases?

Rheumatoid Arthritis

In people with rheumatoid arthritis, the immune system predominantly targets the lining (synovium) that covers various joints. Inflammation of the synovium is usually symmetrical (occurring equally on both sides of the body) and causes pain, swelling, and stiffness of the joints. These features distinguish rheumatoid arthritis from osteoarthritis, which is a more common and degenerative "wear-and-tear" arthritis.



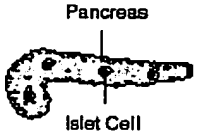
An inflamed joint—the synovium—is attacked by cells and molecules of the immune system.

Currently available therapy focuses on reducing inflammation of the joints with anti-inflammatory or immunosuppresssive medications. Sometimes, the immune system may also target the lung, blood vessels, or eye; occasionally patients may also develop symptoms of other autoimmune diseases such as Sjogren's the inflammation, itching, and scaling. For more severe cases, oral medications are used. Psoriasis is common and may affect more than 2 out of 100 Americans. Psoriasis often runs in families.

Multiple Sclerosis

Multiple sclerosis is a disease in which the immune system targets nerve tissues of the central nervous system. Most commonly, damage to the central nervous system occurs intermittently, allowing a person to lead a fairly normal life. At the other extreme, the symptoms may become constant, resulting in a progressive disease with possible blindness, paralysis, and premature death. Some medications such as beta interferon are helpful to people with the intermittent form of multiple sclerosis.

In young adults, multiple sclerosis is the most common disabling disease of the nervous system. Multiple sclerosis afflicts 1 in 700 people in this country. Researchers continue to search for triggers of the disease.



Immune-Mediated or Type 1 Diabetes Mellitus

Type 1 diabetes mellitus results from autoimmune destruction of the insulin-producing cells of the pancreas. Insulin is required by the body to keep the blood sugar (glucose) level under control. High levels of glucose are

responsible for the symptoms and the complications of the disease. However, most of the insulin-producing cells are destroyed before the patient develops symptoms of diabetes. Symptoms include fatigue, frequent urination, increased thirst, and possible sudden confusion.

Type 1 diabetes mellitus is usually diagnosed before the age of 30 and may be diagnosed as early as the first month of life. Together with Type 2 diabetes (not considered an autoimmune disease), diabetes mellitus is the leading cause of kidney damage, loss of eyesight, and leg amputation. Close control of sugar levels decreases the rate at which these events occur. There is a genetic predisposition to Type 1 diabetes, which occurs in 1 out of 800 people in the United States. Among individuals who have a close relative with Type 1 diabetes, those at high risk for developing disease can be identified. Efforts are now under way to evaluate prevention strategies for these family members at risk.

Inflammatory Bowel Diseases

This medical term is used for both Crohn's disease and ulcerative colitis, two diseases in which the immune system attacks the gut (intestine). Patients may have diarrhea, nausea, vomiting, abdominal cramps, and pain that can be difficult to control. Illness in afflicted individuals can result from intestinal inflammation and from side effects of the drugs used for the disease. For example, daily use of high-dose corticosteroid (prednisone) therapy, which is needed to control severe symptoms of Crohn's disease, can predispose patients to infections, bone thinning (osteoporosis), and fractures. For patients with ulcerative colitis, surgical removal of the lower intestine (colon) will eliminate the disease and their increased risk for colon cancer. More than 1 in 500 Americans has some type of inflammatory bowel disease.

Sunlight is one of the triggers of lupus and can worsen the progression of the disease.

Systemic Lupus Erythematosus

Patients with systemic lupus erythematosus most commonly experience profound fatigue, rashes, and joint pains. In severe cases, the immune system may attack and damage several organs such as the kidney, brain, or lung. For many individuals, symptoms and damage from the disease can be controlled with available anti-inflammatory medications. However, if a patient is not closely monitored, the side effects from the medications can be quite serious. Lupus occurs in 1 out of 2,000 Americans and in as many as 1 in 250 young, African-American women.

Psoriasis

Psoriasis is an immune system disorder that affects the skin, and occasionally the eyes, nails, and joints. Psoriasis may affect very small areas of skin or cover the entire body with a buildup of red scales called plaques. The plaques are of different sizes, shapes, and severity and may be painful as well as

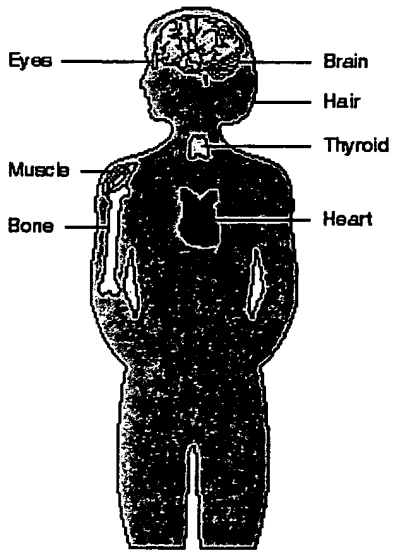
unattractive. Bacterial infections and pressure or trauma to the skin can aggravate psoriasis. Most treatments focus on topical skin care to relieve the inflammation, itching, and scaling. For more severe cases, oral medications are used. Psoriasis is common and may affect more than 2 out of 100 Americans. Psoriasis often runs in families.

Scleroderma

This autoimmune disease results in thickening of the skin and blood vessels. Almost every patient with scleroderma has Raynaud's, which is a spasm of the blood vessels of the fingers and toes. Symptoms of Raynaud's include increased sensitivity of the fingers and toes to the cold, changes in skin color, pain, and occasionally ulcers of the fingertips or toes. In people with scleroderma, thickening of skin and blood vessels can result in loss of movement and shortness of breath or, more rarely, in kidney, heart, or lung failure. The estimated number of people with any type of scleroderma varies from study to study but may range from 1 to 4 affected individuals for every 10,000 Americans (or as many as 1 out of 2500 individuals).

Autoimmune Thyroid Diseases

Hashimoto's thyroiditis and Grave's disease result from immune system destruction or stimulation of thyroid tissue. Symptoms of low (hypo-) or overactive (hyper-) thyroid function are nonspecific and can develop slowly or suddenly; these include fatigue, nervousness, cold or heat intolerance, weakness, changes in hair texture or amount, and weight gain or loss. The diagnosis of thyroid disease is readily made with appropriate laboratory tests.



The thyroid gland affect many parts of the body.

The symptoms of hypothyroidism are controlled with replacement thyroid hormone pills; however, complications from over- or under-replacement of the hormone can occur. Treatment of hyperthyroidism requires long-term anti-thyroid drug therapy or destruction of the thyroid gland with radioactive iodine or surgery. Both of these treatment approaches carry certain risks and

long-term side effects. Autoimmune thyroid diseases afflict as many as 4 out of 100 women and are frequently found in families where there are other autoimmune diseases.

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